INTERGENERATIONAL FACTORS IN CARDIOVASCULAR HEALTH: A PROSPECTIVE COHORT STUDY

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ABSTRACT

Background. Cardiovascular etiologies are complex and influenced by several exposures acting together across the life-course. This dissertation examined the life-course pathways of cardiovascular health in relation to three intergenerational factors. First, we examined associations of genetic risk of higher body mass index (BMI) with BMI development, and whether the genetic associations differ by socioeconomic position (SEP) at different life stages (Study I). Second, we assessed intergenerational associations of ideal cardiovascular health behaviors between parents and their adult offspring, and whether these associations differ by SEP at different life stages (Study II). Third, we evaluated the association of favorable childhood psychosocial environment with adult cardiac structure and function (left ventricular (LV) mass ($g/m^{2.7}$) and LV diastolic function (E/e' ratio) and to which extent ideal cardiovascular health behaviors mediate these associations (Study III).

Methods. Study participants were three subsamples from the prospective intergenerational Cardiovascular Risk in Young Finns Study (n=2441 in Study I, n=1856 in Study II, n=880 in Study III). We used data from follow-ups in 1980, 1983, 1986, 2001, 2007 and 2011. BMI was recorded in all follow-ups across 1980-2011. Genetic risk of BMI was assessed in 2001 with 97 single-nucleotide polymorphisms identified in the most recent GWAS meta-analysis. Four cardiovascular health behaviors – smoking, BMI, physical activity and diet – were recorded following the American Heart Association definitions. SEP was measured as educational attainment, income and occupational status. Adult SEP and health behaviors were self-reported or measured during a study visit in 1986, 2001, 2007 and 2011. Parental SEP and health behaviors were self-reported by parents of study participants in 1980. Childhood environment was assessed with a cumulative score comprising data from six relevant psychosocial domains reported by parents of study participants in 1980. Echocardiographic examination was conducted in 2011.

Statistical analysis. Genetic associations with BMI development were analyzed with multilevel linear regression with random intercepts and random slopes. Intergenerational associations of health behaviors were assessed using ordinal and linear multilevel models with random intercepts. Associations of childhood psychosocial environment with adult cardiac structure and function and mediation pathways through cardiovascular health behaviors were assessed with marginal structural models in the causal mediation analysis framework.

Results. In Study I, mean BMI increased from 22.6 to 26.6 kg/m^2 during the follow-up. In growth curve analyses, the genetic risk score was associated with faster BMI increase over time (b=0.02, 95% CI, 0.01, 0.02 for genetic risk score x age interaction). The genetic associations with BMI were weaker among those with higher (vs lower) educational attainment in adulthood (b=-0.12, 95% CI, -0.23, 0.01 for genetic risk score x adult education interaction). At age 49, compared with those at the 10th percentile of the genetic risk score, those at the 90th percentile had 3.3 units higher predicted BMI at the lowest level of educational attainment and 2.4 units higher BMI at the highest level educational attainment. No interaction effect was observed between the genetic risk score and parental education (b=0.05, 95% CI, -0.09, 0.18 for genetic risk score x parental education interaction).

In Study II, one additional ideal cardiovascular health behavior among parents was associated with 28% higher odds of one additional ideal behavior among offspring (odds ratio (OR)=1.28, 95% CI, 1.17,1.39). Furthermore, ORs for these intergenerational associations were greater among offspring who had higher own adult educational attainment or whose parents had higher educational attainment (OR=1.32 for high vs OR=1.04 for low offspring education; p=0.02 for interaction, OR=1.56 for high vs OR=1.19 for low parental education; p=0.01 for interaction). Similar trends were seen with parental income and offspring occupation. Results from linear regression analyses were similar.

In Study III, favorable psychosocial environment in childhood was associated with more optimal cardiac structure and function in adulthood. Those above the median of the childhood score versus below the median had 1.28 g/m$^{2.7}$ lower LV mass (95% CI=-2.63, 0.07) and 0.18 lower E/e' ratio (95% CI=-0.39, 0.03). There was no evidence of indirect effects from childhood environment to LV outcomes through adult cardiovascular health behaviors after controlling for time-dependent confounding by adult SEP (indirect effect b=-0.30, 95% CI=-1.22, 0.63 for LV mass, b=-0.04, 95% CI=-0.18, 0.11 for E/e' ratio). Results after multiple imputation were similar.

Conclusions. These findings highlight the importance of intergenerational and early-life exposures in initiating pathways of long-term cardiovascular health and suggest these pathways may be shaped by socioeconomic circumstances at different life stages.

TIIVISTELMÄ

Tausta. Useat eri elämänvaiheissa ilmenevät tekijät voivat vaikuttaa sydän- ja verisuoniterveyteen elämän aikana. Tässä väitöskirjassa tutkittiin kolmen ylisukupolvisen tekijän vaikutusta sydän- ja verisuoniterveyden elämänkaarikehitykseen. Ensimmäisessä osatutkimuksessa tarkasteltiin korkeaan painoindeksiin (BMI) yhdistetyn geneettisen riskin yhteyttä BMI:n kehitykseen aikuisuudessa ja sitä, riippuuko geneettisen riskin ja BMI:n välinen yhteys sosioekonomisista tekijöistä eri elämänvaiheissa. Toisessa osatutkimuksessa arvioitiin vanhempien terveyskäyttäytymisten yhteyttä heidän aikuisten lastensa terveyskäyttäytymisiin ja sitä, riippuvatko terveyskäyttäytymisten ylisukupolviset yhteydet sosioekonomisesta asemasta eri elämänvaiheissa. Kolmannessa osatutkimuksessa selvitettiin lapsuuden suotuisan psykososiaalisen ympäristön yhteyttä sydämen rakenteeseen ja toimintaan aikuisuudessa (vasemman kammion massaan ($g/m^{2.7}$) ja vasemman kammion diastoliseen funktioon (E/e' ratio)) ja sitä, missä määrin aikuisuuden terveyskäyttäytymiset selittävät näitä yhteyksiä.

Menetelmät. Tutkimukseen osallistujina oli kolme erillistä otosta prospektiivisesta Lasten Sepelvaltimotaudin Riskitekijät (LASERI) kohorttitutkimuksesta (n=2441 n=1856 ja n=880 osatutkimuksissa I, II ja III). Käytetty aineisto oli kerätty kuudessa seurannassa vuosina 1980, 1983, 1986, 2001, 2007 ja 2011. BMI (kg/m^2) mitattiin tutkimuskäynnillä kaikissa seurannoissa vuosina 1980-2011. Korkealle BMI:lle altistavaa geneettistä riskiä arvioitiin vuonna 2001 97 yhden nukleotidin polymorfismia kattavan geneettisen riskipistemäärän avulla. Neljää terveyskäyttäytymistä – tupakointia, BMI:tä, liikuntaa ja ruokavaliota – arvioitiin American Heart Associationin määritelmien mukaan. Sosioekonomisen aseman arviointiin käytettiin koulutusta, tuloja ja ammattiasemaa. Osallistujat vastasivat kyselyyn terveyskäyttäytymisistään ja sosioekonomisesta asemastaan vuosina 1986, 2001, 2007 ja 2011. Osallistujien vanhemmat vastasivat kyselyyn terveyskäyttäytymisistään ja sosioekonomisesta asemastaan vuonna 1980. Lapsuusympäristöä arvioitiin kuuden psykososiaalisen tekijän kumulatiivisena summana. Psykososiaalisia tekijöitä arvioitiin vanhempien täyttämillä kyselyillä vuonna 1980. Sydämen ultraäänikuvausaineisto kerättiin vuonna 2011.

Tilastolliset analyysit. Geneettisiä yhteyksiä BMI:n kehitykseen arvioitiin kasvukäyrämalleilla ja terveyskäyttäytymisten ylisukupolvisia yhteyksiä ordinaalisilla ja lineaarisilla monitasoregressiomalleilla. Lapsuuden psykososiaalisen ympäristön yhteyksiä sydämen rakenteeseen ja toimintaan terveyskäyttäytymisten kautta tarkasteltiin marginaalisilla rakennemalleilla kausaalisen mediaatioanalyysin viitekehyksessä.

Tulokset. Osatutkimuksen I kasvukäyrämallien perusteella BMI:n keskiarvo kohosi otoksessa seurannan aikana (22.6 BMI-yksiköstä 26.6 BMI-yksikköön) ja korkeampi geneettinen riskipistemäärä oli yhteydessä nopeampaan BMI:n kasvuun (geneettisen riskipistemäärän ja iän interaktio b=0.02, 95% CI, 0.01, 0.02). Geneettiset yhteydet olivat heikompia korkeamman (vs. matalamman) koulutuksen aikuisiässä saavuttaneilla osallistujilla (geneettisen riskipistemäärän ja koulutuksen välinen interaktio b=-0.12, 95% CI, -0.23, 0.01). Ero geneettisen riskipistemäärän 10. ja 90. persentiilin välillä oli 3.3 BMI-yksikköä matalimman koulutuksen tasolla ja 2.4. BMI-yksikköä korkeimman koulutuksen tasolla 49 vuoden iässä. Geneettiset yhteydet eivät eronneet toisistaan osallistujien vanhempien koulutuksen eri tasoilla (geneettisen riskipistemäärän ja vanhempien koulutuksen välinen interaktio b=0.05, 95% CI, -0.09, 0.18).

Osatutkimuksessa II vanhempien terveyskäyttäytymiset olivat yhteydessä heidän lastensa aikuisiän terveyskäyttäytymisiin (OR=1.28, 95% CI, 1.17,1.39). Optimaalisten terveyskäyttäytymisten ylisukupolviset yhteydet olivat suurempia korkeammin koulutetuilla osallistujilla (OR=1.32 korkeimmin vs. OR=1.04 matalimmin koulutetuilla; interaktio p=0.02), ja osallistujilla, joiden vanhemmilla oli korkeampi koulutus (OR=1.56 korkeimmin vs. OR=1.19 matalimmin koulutettujen vanhempien lapsilla; interaktio p=0.01). Samanlaisia eroja ylisukupolvisissa yhteyksissä havaittiin osallistujien aikuisuuden ammattiaseman ja heidän vanhempiensa tulotason suhteen. Ordinaali- ja lineaarimallien tulokset olivat samanlaiset.

Osatutkimuksessa III suotuisa psykososiaalinen lapsuusympäristö oli yhteydessä optimaalisempaan sydämen rakenteeseen ja toimintaan aikuisiässä. Erot lapsuusympäristön suotuisuutta ilmaisevan pistemäärän mediaanin ylä- ja alapuolelle sijoittuvien osallistujien välillä olivat 1.28 g/m$^{2.7}$ vasemman kammion massassa (95% CI=-2.63, 0.07) ja 0.18 E/e' ratiossa (95% CI=-0.39, 0.03). Lapsuusympäristön yhteys sydämen rakenteeseen ja toimintaan ei selittynyt aikuisiän terveyskäyttäytymisillä, kun aikuisiän sosioekonominen asema oli otettu huomioon. Tulokset olivat samanlaiset imputoidussa aineistossa.

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LIST OF ORIGINAL PUBLICATIONS

I Komulainen K, Pulkki-Råback L, Jokela M, et al. Education as a moderator of genetic risk for higher body mass index: Prospective cohort study from childhood to adulthood. *Int J Obes*. 2018;42(4):866-871. http://dx.doi.org/10.1038/ijo.2017.174.

II Komulainen K, Mittleman MA, Jokela M, et al. Socioeconomic position and intergenerational associations of ideal health behaviors. Eur J Prev Cardiol. 2019;26(15):1605-1612. doi: 10.1177/2047487319850959.

III Komulainen K, Mittleman MA, Pulkki-Råback L, et al. Childhood psychosocial environment and adult cardiac outcomes: A causal mediation approach. *Am J Prev Med*. 2019;57(6):e195−e202.

The publications are referred to in the text by their Roman numerals.

LIST OF ABBREVIATIONS

AHA	American Heart Association
BA	Bachelor's degree
BMI	Body mass index
CI	Confidence interval
GWAS	Genome-wide association study
LV	Left ventricular
MA	Master's degree
OR	Odds ratio
SD	Standard deviation
SE	Standard error
SEP	Socioeconomic position
SNP	Single-nucleotide polymorphism
YFS	The Cardiovascular Risk in Young Finns Study

1 INTRODUCTION

Cardiovascular disease (CVD) kills 17.9 million people each year, accounting for a third of all deaths worldwide.[1] Almost half of these deaths occur prematurely before the age of 70.[2] Apart from mortality, CVD contributes substantial disability and individual suffering. For the most part CVD is preventable. The World Health Organization (WHO) estimates that eliminating the key modifiable risk factors would prevent 75% of heart disease, stroke and type 2 diabetes.[3]

Despite large-scale efforts to prevent CVD, people are failing to achieve adequate risk factor or therapeutic targets. In the US, the prevalence of CVD is estimated to rise 10% between 2010 and 2030, and the real total direct medical costs of CVD are projected to increase from $273 billion in 2010 to $818 billion in 2030.[4] This increase in CVD prevalence is partially due to population aging, but also the dramatic lifestyle-induced increases in obesity during the past few decades, and obesity-associated increases in the prevalence of hypertension, diabetes and physical inactivity. WHO projects sharp rises in the prevalence of obesity all across Europe by 2030, even in the Scandinavian countries that typically show low obesity prevalence.[5] During the past two decades, the absolute number of CVD cases has increased in Europe and within the EU.[6] More than 85 million people in Europe were living with CVD in 2015, with annual costs of €210 billion to the EU economy at present.[6] Worldwide, the number of CVD-related deaths is projected to increase to almost 24 million by 2030, most of them occurring low and middle income countries.[7] Thus cardiovascular disease is a global public health priority.

1.1 Life-course approaches to cardiovascular health

While CVD rarely manifests clinically before adulthood, the pathogenic process determining later risk of CVD takes place over decades. Adult cardiovascular endpoints are shaped by influences occurring at multiple life stages and acting together across life.[8] Similarly opportunities for CVD prevention can occur at different stages of life – epidemiologic approaches that elucidate the life-course development of CVD thus represent a prominent viewpoint to examining cardiovascular etiologies.

Life-course epidemiology examines the long-term effects on later health or disease risk of a variety of physical and social exposures occurring at different life stages – from gestation to adult life and across generations.[9] Given the massive shifts in lifestyle affecting the developmental environments of people born during the recent decades, the life-course perspective represents a relevant

interdisciplinary account to uncover long-term pathways of cardiovascular health in the population. Longitudinal cohort studies offer means for this investigation by providing prospective, repeated-measures data recorded at different stages of an individual's life and across generations.[8]

This dissertation draws on the life-course framework to examine the development cardiovascular health and disease using prospective data from the Cardiovascular Risk in Young Finns Study. We aim to elucidate some important intergenerational mechanisms that potentially underlie the long-term development of CVD. Here, we use the term *intergenerational* to broadly refer to influences that exist and occur across generations – CVD-relevant exposures or wider contextual influences that parents may pass on to their offspring – which have been associated with long-term trends of cardiovascular health in the population.

Several intergenerational exposures can determine the course of CVD and CVD risk factors over time. First, genetic factors inherited from parents play a role in CVD etiologies and have been shown to have incremental predictive value beyond traditional CVD risk factors.[10–15] Apart from genetics, intergenerational influences can occur more broadly. Key behavioral risk factors of CVD, such as smoking, poor diet or physical inactivity, originate in family environments as children are exposed to behavioral patterns of their parents.[16–21] Health behaviors adopted in childhood and youth have been shown to remain relatively stable in later life stages,[22–25] and thus these intergenerational chains of health behaviors may represent one important mechanism explaining long-term trends in cardiovascular health. Also, wider contextual experiences occurring in and created by an individual's childhood family have been associated with the later-life cardiovascular health, with heightened risk of CVD associated with adverse environments.[26–29] In particular, the role of psychosocial factors in childhood and youth is recently widely acknowledged and gaining increasing attention in epidemiologic research.[26–35]

These three different phenomena – genetic contributions, intergenerational continuum of health behaviors, and early-life psychosocial determinants of later cardiovascular outcomes – represent the starting point for the three sub-studies of this dissertation. A more detailed rationale of study is outlined in the following sections.

1.1.1 Genetics

Rapid advances in genetics research during the past decade have brought novel data on the genetic risk factors underlying CVD.[36] While early studies in genetic epidemiology attempted to identify

single genes explaining molecular genetic risks for illnesses, most chronic diseases are complex, involving action of hundreds or thousands of genes. Recent genome-wide association studies (GWAS) and GWAS meta-analyses have identified numerous novel genetic loci associated with between-individual differences in cardiovascular phenotypes.[36] The identified genetic variants – single-nucleotide polymorphisms (SNP) occurring in the DNA – have been combined into polygenic risk scores that summarize the trait-relevant information across the genome.[37] Although the risk scores explain but a minor proportion of the estimated heritability of cardiovascular phenotypes, they have been shown to have incremental predictive value when considered together with traditional cardiovascular risk factors.[10–13]

Furthermore, the expression of genetic predisposition may depend on environmental exposures. In genetic epidemiology, this is called a gene-environment interaction – phenotype resulting from genetic risk is modified by environment.[38] Understanding such modification is important as it can inform us about environmental means to mitigate genetic risks which by themselves are non-reversible. In terms of CVD risk factors, much attention has recently been devoted to environments that regulate the phenotypic expression of genetic risk of BMI. Several large-scale studies have suggested that the genetic risk of BMI is associated with higher BMI more strongly in obesogenic environments.[39–44] For instance, stronger genetic associations with BMI have been reported among people who consume high-fat fried foods[41] or sugar-sweetened beverages,[40] or who are physically inactive.[42,43]

Obesogenic exposures are more prevalent among socioeconomically disadvantaged population segments[45–47] and thus socioeconomic position (SEP) has been suggested as a surrogate measure that can capture several aspects of the obesogenic environment.[39] Some evidence has suggested that socioeconomic differences modify the phenotypes resulting from genetic risk,[39,48–50] but there is limited data on the timing of this effect measure modification. Both twin studies and studies using GWAS data on genetic risk have suggested socioeconomic conditions in adulthood modify genetic associations with BMI.[39,48–50] By contrast, studies have yielded inconsistent findings as to whether genetic associations may already be modified by childhood socioeconomic environments.[48,51] Understanding the role of SEP in shaping genetic associations at different life stages is relevant for prevention – it can help direct interventions to at-risk individuals at most effective ages across life.

1.1.2 Intergenerational associations of health behaviors

Health behaviors, such as smoking, physical activity and diet, are recognized as key determinants of cardiovascular health and major reversible targets in CVD prevention.[52–56] Health behaviors of parents are known to correlate with health behaviors of their offspring[16–21] and several studies have documented that behavioral patterns adopted in childhood and youth track into adulthood.[22–25] Most previous research examining intergenerational associations of health behaviors has focused on single behavior-related risk factors such as smoking or BMI. However, health behaviors are often clustered within individuals, and simultaneous adherence to several optimal behaviors is known to reduce cardiovascular risk.[52–54,56]

To promote optimal behaviors across generations, it is crucial to identify factors that may enhance or attenuate the intergenerational associations of health behaviors. Socioeconomic differences – both in childhood and in adulthood – have been consistently associated with differences in health behaviors, with optimal behavioral patterns more often found among people with higher SEP. [45–47] Some studies have suggested that parental SEP may affect how health behaviors are passed on from parents to their offspring, but the evidence is not conclusive.[19,57,58] Moreover, data are sparse on the role of SEP at different life stages in modifying the intergenerational associations, although this knowledge is potentially relevant to long-term health promotion. If upward social mobility, i.e. offspring attaining higher SEP than their parents would enhance the intergenerational continuum of optimal behaviors, it would suggest the effects of behavioral risk factors occurring and adopted in early life stages might be counteracted by socioeconomic achievement decades later.

1.1.3 Childhood psychosocial environment

Apart from direct transfer of CVD risk factors across generations, the development of CVD may be influenced by a broader family environment. While several studies have shown that early-life psychosocial adversity is associated with cardiovascular risks in adulthood,[26–28] recent investigations have turned the focus toward favorable psychosocial factors that may help maintain optimal cardiac health.[30–35] Adult cardiovascular health has been linked to various early-life psychosocial factors, including family socioeconomic position,[59,60] emotional climate,[61,62] health behaviors,[63,64] environmental safety and stability,[26,65] and child's self-regulation skills.[35,66,67] In the Cardiovascular Risk in Young Finns Study, favorable psychosocial environment in childhood and adolescence was associated with lower risk of type II diabetes[30] and coronary artery calcification,[32]

more optimal BMI development[33] and a more ideal overall cardiovascular profile.[31] Similar findings have been reported in US cohorts[35,61]

Favorable childhood environment may influence cardiovascular outcomes through direct biological pathways, e.g., by supporting optimal regulation of immune, metabolic, neuroendocrine and autonomic nervous systems[68] and enhancing restorative physiological processes.[34] Childhood environment may also influence cardiovascular health through behavioral pathways. For instance, adverse childhood environment has been associated with smoking, overweight, physical inactivity and substance use in adulthood,[27,69] that in turn are associated with cardiovascular outcomes.

If behavioral factors lie on the causal pathway from childhood conditions to later-life cardiovascular health, they can also represent a modifiable means to reverse adverse effects of early-life psychosocial insults. However, the amount of association of childhood environment with adulthood cardiac outcomes that causally operates through adult health behaviors is not well known. Longitudinal cohort studies represent the most viable means to assess such mediation effects in life-course perspective, but at the same time they are limited in establishing causality.[70] With recent methodological advances, new techniques are available for addressing causal questions in observational data to contribute evidence on mediation pathways from childhood exposures to outcomes in later life stages.[70] Such evidence is relevant to cardiovascular health improvement strategies.

2 STUDY AIMS

Several intergenerational factors can be relevant to the development of cardiovascular health over the life-course. Associations of genetic, behavioral and psychosocial determinants with cardiovascular risk factors and outcomes are documented. Still, important questions remain in terms of for whom, when and how the intergenerational risk and protective factors occur. This dissertation aims to present observational evidence to elucidate these questions.

Aims

1.1 To evaluate the association of the 97-SNP genetic risk score for BMI with the age-dependent development of BMI from young adulthood to midlife

1.2 To examine whether genetic associations differ across levels of childhood or adult SEP

2.1 To assess the intergenerational associations of cardiovascular health behaviors between parents and their offspring

2.2. To examine whether these intergenerational associations differ across levels of childhood and adult SEP

3.1 To evaluate the associations of childhood psychosocial environment with cardiac structure and function

3.2 To determine the extent to which, if any, these associations are causally mediated through adult cardiovascular health behaviors

Hypotheses

1.1 Higher genetic risk is associated with faster age-dependent increase in BMI during adulthood

1.2 Higher own adult or parental SEP mitigates the expression of the genetic risk of higher BMI

2.1 Ideal cardiovascular health behaviors of parents are associated with ideal cardiovascular health behaviors of their offspring

2.2 Higher own adult or parental SEP strengthens the intergenerational associations of ideal health behaviors

3.1 Favorable childhood psychosocial environment is associated with more optimal cardiac structure and function in adulthood

3.2 These associations are partially explained by ideal cardiovascular health behaviors in adulthood

3 METHODS

3.1 Data

The Cardiovascular Risk in Young Finns (YFS) study is an ongoing prospective cohort study on the risk factors and precursors of CVD. The study was started in 1980, when 3596 children and adolescents (aged 3, 6, 9, 12, 15 and 18) participated in the first cross-sectional study phase. The participants were enrolled from five geographical areas representing all parts of Finland using random-sampling from the national register. Follow-ups have been conducted regularly to date. In addition, parents of the study participants filled in questionnaires of their own cardiovascular health status, health behaviors and socioeconomic factors at the study inception in 1980. The study has been conducted in accordance to the Declaration of Helsinki and it is approved by local ethics committees. All participants gave written informed consent.[71]

3.2 Participants

In Study I, the genetic risk score was available for 2443 individuals who also had data on parental educational attainment in 1980 or at least one measurement of own educational attainment in 1986, 2001, 2007 or 2011. Of the 2443 participants, we excluded two individuals due missing data on adult BMI (assessed at age >18) at all follow-ups in 1980, 1983, 1986, 2001, 2007 and 2011 (**Table 1)**. This left a study population of 2441.

A total of 2345 YFS participants met the inclusion criterion for **Study II** as they had data on parental health behaviors and parental educational attainment in 1980. Of the 2345 participants initially eligible, we excluded 293 due to missing data on adult educational attainment at all follow-ups in 2001, 2007 and 2011, and an additional 196 due to missing data on adult health behaviors at all follow-ups in 2001, 2007 and 2011 (**Table 1**), leaving a study population of 1856.

Study III included 2067 participants who had data on childhood psychosocial environment and who were thus initially eligible. Of these 2067, we excluded 864 to missing behavioral and covariate data in 2001 and additional 323 due to missing data on LV mass and diastolic function from 2011 (**Table 1**), which left a study population of 880.

Table 1. The Cardiovascular Risk in Young Finns Study waves used in Studies I-III

	1980	1983	1986	2001	2007	2011
Study I						
Genetic risk score				●		
Parental education	●					
Adult education			●	●	●	●
Diet			●	●	●	●
Physical activity			●	●	●	●
Body mass index	●	●	●	●	●	●
Study II						
Parental health behaviors	●					
Parental education	●					
Parental income	●					
Parental occupation	●					
Offspring health behaviors				●	●	●
Offspring education				●	●	●
Offspring income					●	●
Offspring occupation				●	●	●
Study III						
Childhood psychosocial environment	●					
Adult health behaviors				●	(●)	
Left ventricular mass						●
E/e' ratio						●

3.3 Measures

3.3.1 BMI (Study I)

BMI was measured during a study visit at six follow-ups (1980, 1983, 1986, 2001, 2007 and 2011) as weight (kg) divided by height (m^2). Weight was measured in light clothing without shoes to the nearest 0.1 kg. Height was measured with a wall-mounted stadiometer to the nearest 0.5 cm.

3.3.2 Genetic risk score for BMI (Study I)

Genetic risk for BMI was measured in 2001 based on 97 SNPs identified in the most recent genome-wide association study (GWAS) meta-analysis.[15] A genetic risk score was calculated as the sum of genotyped risk alleles (0/1/2) or imputed allele dosages of the 97 SNPs, weighted by the effect sizes reported in the GWAS meta-analysis.[15] Genotyping was performed with the Illumina

Bead Chip (Human 670K). Genotype imputation was performed in two stages: haplotype phasing was done using SHAPEIT v1 and genotype imputation using IMPUTE2 and 1000 Genomes Phase I Integrated Release Version 3 (March 2012 haplotypes) as a reference. There were 58 imputed and 39 directly genotyped SNPs. Average imputation quality for imputed SNPs was 0.9877 (range 0.8218-1). In genetic risk score formation effect allele dosages were calculated from imputed genotype probabilities to incorporate the degree of uncertainty of imputed SNPs. Standardized scores of the genetic risk score were used in all analyses. High and low genetic risk were defined at the 10^{th} and 90^{th} percentiles of the genetic risk score (mean ±1.28 standard deviations (SD)).

3.3.3 Socioeconomic position (Studies I-III)

SEP was assessed with three indicators – educational attainment (Studies I-III), income (Study II) and occupational status (Study II). Educational attainment was used as a primary measure of SEP as it remains relatively stable over time and is an indicator of SEP that is strongly associated with health behaviors and cardiovascular outcomes.[46,72,73]

Participant SEP

Data on adult SEP was collected through participant self-reports in 1986, 2001, 2007 and 2011. *Educational attainment* (highest level of educational attendance or completed education) was categorized in four groups: primary education; secondary education; Bachelor's degree program or equivalent; Master's degree program or higher. In Study III a dichotomous measure of educational attainment was used (no college (primary/secondary) vs. some college (Bachelor's degree program or higher). *Gross income* was measured on a 7-point scale ranging from 0 (annual income of 0-10000 EUR) to 6 (annual income of >60000 EUR). *Occupational status* was classified into manual, lower non-manual and higher non-manual (0/1/2) according to the classification of Statistics Finland.

Parental SEP

Data on parental SEP was collected through parents' self-reports at study inception in 1980. *Parental educational attainment* (measured as completed years of schooling) was categorized into four groups: ≤9 years; 10-12 years; 13-15 years; >15 years. In two-parent families, data from the more educated parent was used, and we also looked at mother's and father's educational attainment separately. *Parental income* was measured as the previous year's household gross income in Finnish marks on a 7-point scale ranging from 0 (0-25000 FIM) to 6 (> 100000 FIM) in 1980 (1 FIM in 1979 corresponds to ca 0.56 EUR in 2019). *Parental occupational status* was classified into

manual, lower non-manual and higher non-manual according to the classification of Statistics Finland. In two-parent families, data from the parent with higher occupational status was used.

3.3.4 Cardiovascular health behaviors (Studies I-III)

Participant's ideal health behaviors (Studies I and II)

We used the American Heart Association (AHA) 2020 Strategic Impact Goal guidelines to assess four ideal cardiovascular health behaviors – smoking, BMI, physical activity and diet.[55] Following the AHA definition, we refer to BMI as a behavior in this context, although BMI naturally is not a behavior but a marker determined by genetic and behavioral factors. The data on cardiovascular health behaviors were collected from participants in 1986, 2001, 2007 and 2011. Smoking, physical activity and diet were self-reported. BMI was measured during a study visit as weight (kg) divided by height (m^2). Criteria for ideal smoking status, BMI and physical activity were met if the participant never smoked or quit >1 year ago; had a BMI <25 kg/m^2; engaged in 120 min/week moderate-intensity or 60 min/week vigorous-intensity activity or a combination.[74–76] In 2007 and 2011, ideal diet was defined comprising 4/5 ideal dietary components based on a food-frequency questionnaire (FFQ) on frequency and portion size (semi-quantitative FFQ) and scaled for caloric intake: ≥450 g/day of fruits and vegetables; ≥two servings (100 g) of fish/week; ≥three servings (30 g) of whole grain rye bread/day; <1500 mg of sodium/day; ≤450 kcal of sugar-sweetened beverages/week.[55] In 1986 and 2001, ideal diet was defined comprising 2/3 components based on an FFQ on frequency (non-quantitative FFQ): fruits and vegetables every day; fish ≥2 times/week; and soft drinks ≤2 times/week.[74–76]

In Study I, we used dichotomous measures of ideal diet and ideal physical activity (vs non-ideal diet and non-ideal physical activity) recorded at four follow-ups (in 1986, 2001, 2007 and 2011). In Study II, we assessed the total number of ideal health behaviors at three follow-ups (in 2001, 2007 and 2011). The total number of ideal behaviors was calculated as the count of ideal scores on smoking, BMI, physical activity and diet and thus ranged from 0 to 4. In Study III, we used a dichotomous measure of the total number of ideal health behaviors (<2 vs. ≥2 behaviors) measured in 2001.

Parental ideal health behaviors (Study II)

Data on parental health behaviors were self-reported by parents at study inception in 1980. Criteria for ideal smoking status, BMI and physical activity were met if the parent never smoked or quit >1 year ago; had a BMI < 25 kg/m^2; and exercised regularly at least once a week. As no satisfactory

measurement was available for parental diet in 1980, we used dietary information measured from the participants in 1986 as a proxy for family food environment. Ideal family diet was defined as diet comprising 2/3 dietary components based on an FFQ on frequency (non-quantitative FFQ): fruits and vegetables every day; fish ≥2 times/week; and soft drinks ≤2 times/week.[74–76]

The total number of ideal health behaviors was calculated as the sum of the parental scores on smoking, BMI, physical activity and diet. In two-parent families, each parent contributed separately so that scales of smoking, BMI and physical activity ranged from 0 to 2 (0 – non-ideal behavior in both parents, 1 – ideal behavior in only one parent, 2 – ideal behavior in both parents). Diet was assessed on a two-point scale (0 – non-ideal diet in the family, 2 – ideal diet in the family). The total number of parental ideal health behaviors ranged thus from 0 to 8.

3.3.5 Echocardiography (Study III)

Echocardiograms were performed in 2011. Standard echocardiographic examinations[77,78] were produced from the standardized image planes and modes: parasternal long and short axis in 2-dimensional and M-mode and apical 4-chamber view.[77] Left ventricular mass was calculated as (0.8[1.04((LV end-diastolic diameter + posterior wall thickness + interventricular septum thickness)^3 – LV end-diastolic diameter)^3] + 0.6 g, and it was indexed by height raised to the allometric power of 2.7 (indexed LV mass = LV mass/height$^{2.7}$) as this indexation performs better in the context of overweight and obesity.[78,79] LV diastolic function in the LV filling pressure was measured by using E/e' ratio (higher values indicating lower diastolic function), assessed with continuous and pulsed-wave Doppler measuring transmitral flow and tissue velocities.[77,78]

3.3.6 Childhood psychosocial environment (Study III)

We assessed six factors of childhood psychosocial environment: socioeconomic environment, emotional environment, parental health behaviors, stressful events, child's self-regulation and social adjustment.[30–33] These data were collected from parents of the study participants at the study inception in 1980 via questionnaires. The six psychosocial factors were constructed from several dichotomous variables (0/1). For this purpose, continuous data were first dichotomized. The selection of cutoffs is described below and in **Table 2** (see Pulkki-Råback et al.[31] for details).

1. Favorable socioeconomic environment comprised 4 components: upper white collar occupation (1 point), academic/college degree (1 point), family income in the highest 25% (1 point)

Table 2. Process chart of the construction of the childhood psychosocial factors score

Factor	Definition of favorable level	Absent	Present
Favorable socioeconomic environment			
Occupational status	Upper white collar[a]	0	1
Educational level	Academic or college degree[a]	0	1
Family income	Annual income in the highest quartile	0	1
Occupational stability	Steady employment[b]	0	1
Favorable emotional environment			
Parental mental health	Free of diagnosis for mental disorder[b]	0	1
Parental nurturance	High nurturance[c]	0	1
Parental life satisfaction	High satisfaction[c]	0	1
Reasonable alcohol use	Intoxication ≤3-4 times/year[b]	0	1
Optimal health behaviors of parents			
Energy intake (mother)	Body-mass index <30.0	0	1
Energy intake (father)	Body-mass index <30.0	0	1
Smoking (mother)	No daily smoking	0	1
Smoking (father)	No daily smoking	0	1
Physical activity (mother)	Exercise ≥1 times per week	0	1
Physical activity (father)	Exercise ≥1 times per week	0	1
Lack of stressful events			
Stability of living environment	No change of residence during youth	0	1
Stability of school environment	No change of school during youth	0	1
Stability of family environment	No parental divorce or separation	0	1
Loss of significant persons	No death of family member	0	1
Health-related events	No long-term hospitalization/disease[a]	0	1
Self-regulatory behavior of the child			
Self-control scale	High ability to tolerate frustration	0	1
Aggression control	(1) Doesn't fight	0	1
	(2) Doesn't hit	0	1
	(3) Doesn't need much discipline	0	1
	(4) Doesn't swear	0	1
	(5) Other children haven't complained	0	1
	(6) Other parents haven't complained	0	1
Social adjustment of the child			
Social adjustment scale	(1) Not worried about my child	0	1
	(2) I consider my child as well adjusted	0	1

[a] Either parent had to meet this criterion.

[b] Both parents had to meet this criterion.

[c] Main caregiver replied in 2-parent households; the available parent replied in single-parent households.

and occupational stability (no unemployment spells/retirement due to disability/long-term sick-leave) (1 point). Thus the scale ranged from 0 to 4.

2. Favorable emotional environment comprised 4 components: absence of previously diagnosed parental mental disorder (1 point), high parental nurturance (1 point), high parental life satisfaction (1 point), and reasonable alcohol use of both parents (1 point for intoxicated never or maximum 3-4 times/a year).[80] Altogether the scale range was 0 to 4.

3. Optimal health behaviors of parents were reported independently by each parent. As data on parental diet was not available, BMI >30 kg/m^2 was used as a proxy of excess energy intake (1 point for non-obesity). Other health behaviors were being a nonsmoker (1 point) and regular physical activity (1 point). Mother's and father's health behaviors were summed together. Thus the scale ranged from 0 to 6.

4. Lack of stressful events included events that may threaten a child's sense of stability and continuity. These were moving residence, changing school, parental divorce or separation, death of a family member and serious disease in the family. Non-presence of each gave 1 point. Thus the scale ranged from 0 to 5.

5. Self-regulatory behavior of the participant consisted of 2 scales measuring high self-control and high aggression control. The self-control scale consisted of 1 question. Children described as being very controlled "always or most of the time" received 1 point. Aggression control (α=0.60) was measured with 6 dichotomous items, each giving 1 point. The total score was formed by combining scores from self-control and aggression control. Thus the scale ranged from 0 to 7.

6. Social adjustment was assessed by a dichotomous question about parental worry about the child's adjustment (1 point) and parental evaluation of the child's general level of adjustment (1 point). The social adjustment scale ranged from 0 to 2.

The scores from these six domains were standardized (z-scores) and then summed together. Thus, the favorable psychosocial factors score represents the cumulative score of the 6 psychosocial factors, each contributing equal weight.[31] The favorable psychosocial factor score was treated both as a continuous score and a dichotomous variable with a cutoff at the 50th percentile in the analysis.

3.3.7 Confounders

Age and sex were self-reported by participants and adjusted for in all analyses. To control for

cohort effects, we additionally adjusted for the year of follow-up in Study I and for birth year in Study II. All analyses of Study II were additionally adjusted for parental education due to established associations of childhood socioeconomic environment with parental and offspring health behaviors and offspring adult SEP.[81–83] The mediation analysis of Study III was adjusted for age, sex and time-dependent confounding by adult educational attainment (see section 3.4.3 for details).

3.4 Statistical analysis

All statistical analyses were conducted with Stata 13.1 (StataCorp, LP, College Station, TX, USA).

3.4.1 Study I

Associations of the genetic risk score with BMI trajectories in adulthood were examined using multilevel linear regression with random intercepts and random slopes. Each participant could contribute up to 6 repeated measurements of BMI (1980, 1983, 1986, 2001, 2007 and 2011) and up to 4 repeated measurements of own education (1986, 2001, 2007 and 2011) in the multilevel dataset. The random intercept component of the regression model took into account the non-independence of within-individual measurements. The random-slope component was added for the linear effect of age to allow different individuals to follow more or less steep BMI trajectories. In addition to fixed linear time effects (age), we included quadratic (age x age) time effects to account for non-linearity of the BMI trajectories in all models. The models were fit using unstructured error covariance matrix including covariances between the intercepts and the slopes.

We first examined the associations of the genetic risk score with BMI trajectories adjusting for age, sex and the year of follow-up. Then, we included two-way interaction terms between the genetic risk score and educational attainment in the fully adjusted models to evaluate whether the genetic associations with mean levels of BMI during follow-up differed across own or parental educational attainment. These tests for the linear component of trend were conducted in separate models for own and parental educational attainment. Additionally, we assessed the interaction effect between the genetic risk score and parental educational attainment among participants <18 years old. We also assessed whether the gene-education interaction effects differed across time by testing the three-way interaction effects with age (genetic risk score x education x age). The three-way interaction effects were not significant (p=0.53 for three-way interactions with own adult education and parental education) so only the two-way interaction terms were retained.[84] To illustrate the interaction effects, we plotted the marginal predictions at the 10^{th} and 90^{th} percentiles of the genetic risk score at the highest and lowest educational attainment categories.

To roughly assess whether adult diet and physical activity explained any of the association of the gene-education interactions effects with BMI trajectories, we additionally adjusted the final models for the main effects of diet and physical activity and their interactions with the genetic risk score. This adjustment was not considered as a formal test of mediation.

To adjust for possible underlying population substructures, we repeated all analyses including the genetic risk score adding the first four principal components calculated from GWAS data.

3.4.2 Study II

We used random-intercept multilevel ordinal logistic regression to assess the intergenerational associations between the number of parental ideal cardiovascular health behaviors and the odds of their offspring having one additional ideal health behavior. Each participant could contribute up to three measurements of adult health behaviors and SEP. We examined the associations of parental ideal health behaviors with offspring ideal behaviors adjusting for sex, birth year, age, parental education and an interaction term between single-parenthood and parental health behaviors to account for the lower total number of parental health behaviors in single-parent families. We illustrated these results by calculating predicted probabilities of offspring having three or four ideal behaviors (vs fewer) at the 10^{th} and 90^{th} percentile cutoff points of the number of parental ideal health behaviors (i.e. at values 1 and 6). Also, we separately evaluated the associations of both mother's and father's health behaviors with offspring health behaviors in mutually adjusted models. To assess whether the intergenerational associations differed across levels of SEP, we conducted a test for the linear component of trend by including an interaction term between the number of parental ideal health behaviors and SEP in the adjusted models that also included the main effects of parental ideal health behaviors and SEP. These tests for linear trend were conducted in separate models for offspring and parental SEP. Similarly to offspring health behaviors, offspring SEP was measured in 2001, 2007 and 2011 (except income measured in 2007 and 2011). To illustrate the interaction effects, we plotted the odds ratios (OR) for the associations between the number of parental ideal health behaviors and their offspring reporting one additional ideal behavior stratified on levels of SEP. In addition, we separately evaluated the intergenerational associations of health behaviors across mother's and father's educational attainment in mutually adjusted models and compared these interaction effects using the Wald test. We also ran the interaction models using income and occupational status as indicators of SEP.

We conducted additional analyses evaluating the relationship between the number of parental ideal health behaviors and the number of ideal behaviors among offspring modeled as a continuous linear outcome. For these analyses, we used random-intercept linear multilevel regression and plotted the marginal linear predictions for the number of offspring ideal health behaviors at quintiles of parental health behaviors across different levels of SEP. As a sensitivity analysis, we repeated all analyses with a restricted sample that only comprised two-parent families.

Offspring having four ideal behaviors (vs zero) and higher SEP had smaller attrition in each consecutive follow-up in adulthood. Attrition across follow-ups in 2001, 2007 and 2011 was also associated with parental SEP except income, and with parental smoking and BMI. To account for selective attrition, we used pattern mixture modeling.[85] We adjusted all analyses for an attrition indicator expressing the number of times a participant did not contribute to the analysis during the adulthood follow-ups in 2001, 2007 and 2011.

3.4.3 Study III

Linear regression analysis was used to examine the overall associations of the childhood psychosocial factors score with LV mass and diastolic function. LV mass and E/e' ratio were examined in separate models, both without adjustments and adjusted for age and sex. We treated the childhood psychosocial factor score first as a continuous score and scaled the estimates to one standard deviation of the childhood score. Then we assessed the childhood psychosocial factor score as a dichotomous variable and calculated differences in LV mass and E/e' ratio contrasting those above vs below the 50th percentile of the childhood score. Associations of adulthood health behaviors with LV mass and E/e' ratio were assessed in a separate linear regression analysis adjusted for age, sex, adult SEP and the childhood score.

We used a counterfactual approach to assess the natural direct and indirect effects of childhood psychosocial environment on LV outcomes through health behaviors in adulthood. The hypothetical causal model is presented in a directed acyclic graph (**Figure 1**). Here, favorable childhood psychosocial environment is the exposure and ideal health behaviors the proposed mediator. Age and sex were included as potential confounders of both the exposure–outcome and the mediator–outcome associations.[86–92] In addition, we included adult SEP as a potential exposure-induced confounder of the mediator–outcome association. This causal structure was hypothesized based on established associations of childhood psychosocial environment with adult SEP and the associations of adult SEP with both health behaviors and LV structure and function.[46,93,94]

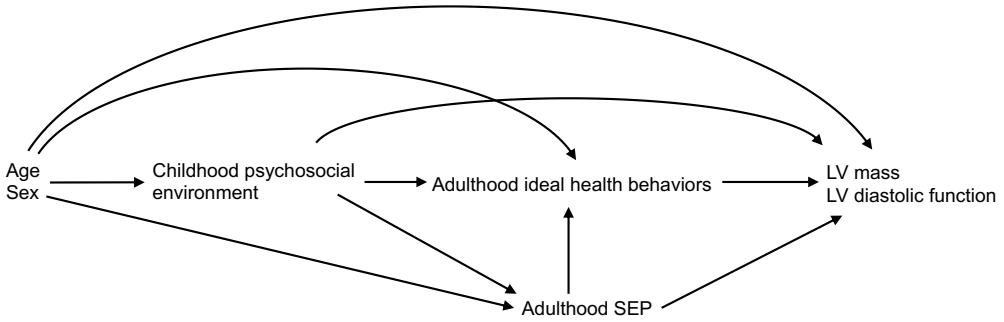

Figure 1. Directed acyclic graph depicting the conceptual model of the relationships between childhood environment, health behaviors and SEP in adulthood and the outcomes of LV mass and diastolic function

Abbreviations: SEP, socioeconomic position; LV, left ventricular

In the presence of exposure-induced confounding, natural direct and indirect effects are not identified, but randomized interventional analogues for the natural direct and indirect effects can be estimated.[70,95] We constructed marginal structural models following the approach described by VanderWeele et al. (2014)[95] that controls confounding by inverse probability weighting. The weights were constructed based on logistic regression models for childhood psychosocial environment, adult SEP and favorable cardiovascular behaviors (all treated as dichotomous variables), and the estimates of direct and indirect effects were obtained from weighted linear regression models regressing the LV outcomes on the exposure. The effect decomposition has been described in detail elsewhere.[95] Standard errors and confidence intervals were obtained with robust variance estimation to account for sampling error in estimating the weights.[96] LV mass and E/e' ratio were analyzed in separate models.

We also performed multiple imputation with chained equations to account for missing data.[97] The imputation model included measures of LV mass, LV diastolic function, educational attainment, ideal health behaviors in 1986, 2001, 2007 and 2011, sex, age and childhood psychosocial factors in 1980. The six psychosocial factors were imputed as separate variables. We imputed all variables with missing data and repeated all analyses in the 10 imputed datasets. Participants with imputed outcomes were excluded from the analysis of imputed data.[97]

4 RESULTS

4.1 Genetic associations with BMI (Study I)

Table 3 shows the characteristics of Study I participants. The 2441 participants (1319 women) who had data on the genetic risk score and own or parental education contributed 7790 person-observations of BMI measurements in the analysis. In 2011, the mean age was 41.9 (SD, 5.0). Mean BMI increased from young adulthood to midlife following a quadratic curve, from 22.6 kg/m^2 (at 18 years) to 26.6 kg/m^2 (49 years) (b=0.31, 95% CI, 0.25 to 0.37 for age, b=-0.003, 95% CI, -0.003 to -0.002 for age squared).

Table 3. Characteristics of 2441 participants in the Cardiovascular Risk in Young Finns Study (Study I)

	Mean (SD)	N [%]
Age in 2011	41.9 (5.0)	
Sex (women)		1319 [54%]
Parental educational attainment (years) in 1980	10.5 (3.6)	
Adult educational attainment in 2011		
Primary		50 [3%]
Secondary		958 [57%]
BA or equivalent		366 [22%]
MA or higher		313 [19%]
Diet in 2011		
Ideal		88 [7%]
Non-ideal		1183 [93%]
Physical activity in 2011		
Ideal		962 [58%]
Non-ideal		691 [42%]
Genetic risk score	0.00 (1.00)	
BMI		
1980	21.4 (2.8)	
1983	21.7 (2.8)	
1986	22.0 (2.8)	
2001	25.0 (4.4)	
2007	26.0 (4.8)	
2011	26.5 (5.0)	

Abbreviations: BMI, body mass index; SD, standard deviation; BA, Bachelor's degree; MA, Master's degree.
Not all percentages add up to 100% due to rounding. Sample sizes with time-varying data do not add up to the total N as not all included individuals contributed data at all study phases.
All time-varying data except for BMI calculated at the latest follow-up in 2011.

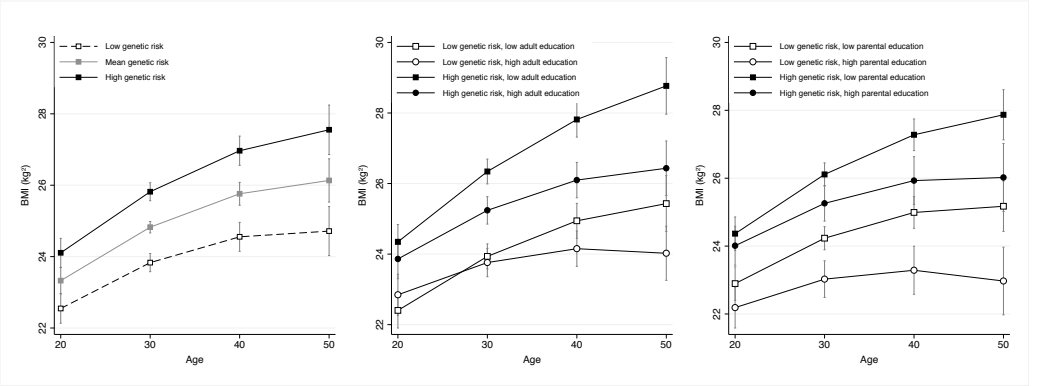

Figure 2. Marginally predicted associations of the 97-SNP genetic risk score with BMI trajectories

Abbreviations: BMI, body mass index. Vertical lines represent 95% confidence intervals. The left panel presents the association of the genetic risk score with BMI trajectories. The middle panel presents the genetic associations with BMI trajectories across levels of participant's own educational attainment. The right panel presents the genetic associations with BMI trajectories across levels of parental educational attainment. Low genetic risk was defined at the 10th percentile and high genetic risk at the 90th percentile of the genetic risk score. Low and high educational attainment refer to the lowest and highest educational attainment categories among participants (primary school vs Master's degree or higher) and their parents (≤9 years vs >15 years of completed schooling).

The genetic risk score was associated with the rate of change in BMI from young adulthood to midlife (b = 0.02, 95% CI, 0.01 to 0.02 for genetic risk score x age interaction). Based on marginal predictions, those at the 90th percentile of the genetic risk score had 1.6, 2.2 and 2.8 kg/m^2 higher BMI at ages of 20, 35 and 49 compared to those at the 10th percentile (**Figure 2**).

Furthermore, the associations of the genetic risk score with mean levels of BMI across the follow-up were weaker among those with higher adult educational attainment compared to lower adult educational attainment (b=0.12, 95% CI, -0.23, -0.01 for genetic risk score x adult education interaction, **Figure 2**). To illustrate these interaction effects, we calculated the marginal predictions for BMI at high (the 90th percentile) and low (the 10th percentile) genetic risk at the highest and lowest level of educational attainment (**Figure 2**). At age 49, compared with those at the 10th percentile of the genetic risk score, those at the 90th percentile had 3.3 units higher predicted BMI at the lowest level of educational attainment and 2.4 units higher BMI at the highest levels educational attainment (both p<0.001, Figure 2). In contrast to findings with adult educational attainment, the associations of the genetic risk score with BMI did not differ across levels of parental educational attainment (b=0.05, 95% CI, -0.09, 0.18 for genetic risk score x parental education interaction).

Table 4. Characteristics of 1856 participants in the Cardiovascular Risk in Young Finns Study and their parents (Study II)

	Mean (SD)	N[%]
Parental characteristics		
Parental educational attainment (years) in 1980	10.9 (3.7)	
Household gross income in 1979 (FIM)	4.0 (1.8)	
≤25000		223 [12.3%]
25001-35000		198 [10.9%]
35001-45000		283 [15.6%]
45001-55000		283 [15.6%]
55001-75000		405 [22.4%]
75001-100000		271 [15.0%]
>100000		149 [8.2%]
Parental occupational status in 1980		
Manual		667 [36.4%]
Lower non-manual		809 [44.2%]
Higher non-manual		355 [19.4%]
Number of parental ideal health behaviors[a]	3.3 (1.6)	
Offspring characteristics		
Sex (female)		1021 [55.0%]
Age in 2001	31.1 (5.0)	
Single-parent family		186 [10.0%]
Study phases with missing data		
None		1176 [63.4%]
1		451 [24.3%
2		229 [12.3%]
Offspring education in 2001	1.8 (0.9)	
Primary		90 [6.1%]
Secondary		534 [36.2%]
BA		419 [28.4%]
MA or higher		432 [29.3%]
Offspring gross income in 2007 (EUR)	3.5 (1.4)	
≤10000		96 [7.3%]
10001-20000		185 [14.0%]
20001-30000		481 [36.3%]
30001-40000		291 [22.0%]
49991-50000		141 [10.6%]
50001-60000		61 [4.6%]
>60000		70 [5.3%]
Offspring occupational status in 2001		
Manual		358 [26.9%]
Lower non-manual		588 [44.1%]
Higher non-manual		387 [29.0%]
Number of offspring ideal health behaviors in 2001[a]	2.0 (1.1)	

Abbreviations: SD, standard deviation; FIM, Finnish mark; EUR, euro; BA, Bachelor's degree; MA, Master's degree.

Time-varying data calculated at the follow-up baseline in 2001 (except for participant income in 2007).

N=1856 persons (3870 person-observations across three study phases).

[a]The number of parental ideal health behaviors ranges from 0 to 8 and offspring ideal health behaviors from 0 to 4.

Additional age-stratified analyses showed no interaction between parental educational attainment and the genetic risk score among those younger than 18 years (n = 2039, b=-0.01, 95% CI, -0.09 to 0.06). All estimates remained similar after adjusting for diet and physical activity (b= -0.10; 95% CI, -0.23 to 0.02 for genetic risk score x adult education, b=0.05, 95% CI, -0.09, 0.19 for genetic risk score x parental education).

To assess whether the genetic associations with the rate of change in BMI over the follow-up differed across levels of educational attainment, we also tested three-way interaction terms between the genetic risk score, educational attainment and age for both adulthood and parental education. These interaction terms were not significant (p=0.53 for both three-way interactions) and they were not included in the final models. All results were similar after adjusting for the first four principal components calculated from the GWAS data to account for possible underlying population substructures.

4.2 Intergenerational associations of cardiovascular health behaviors (Study II)

Table 4 shows the characteristics of Study II participants and their parents. Among participants, there were 1021 (55.0%) women. In 2001, the mean age was 31.1 (SD, 5.0), and the participants had an average of 2.0 (SD, 1.1) ideal health behaviors.

In multilevel ordinal logistic regression models adjusted for the attrition indicator, offspring sex, birth year, age, parental education and the interaction between single-parenthood and parental health behaviors, parental ideal health behaviors were associated with ideal behaviors among offspring (OR=1.28 for each additional ideal behavior among offspring, 95% CI: 1.17, 1.39). Predicted probabilities of offspring having three or four ideal behaviors (vs fewer) were 11.0% at the 10^{th} percentile and 27.1% at the 90^{th} percentile of parental ideal behaviors. The intergenerational associations of ideal health behaviors were of similar magnitude between both mothers and offspring (OR = 1.30, 95% CI: 1.10,1.52) and fathers and offspring (OR = 1.25, 95% CI: 1.09, 1.45) in mutually adjusted models.

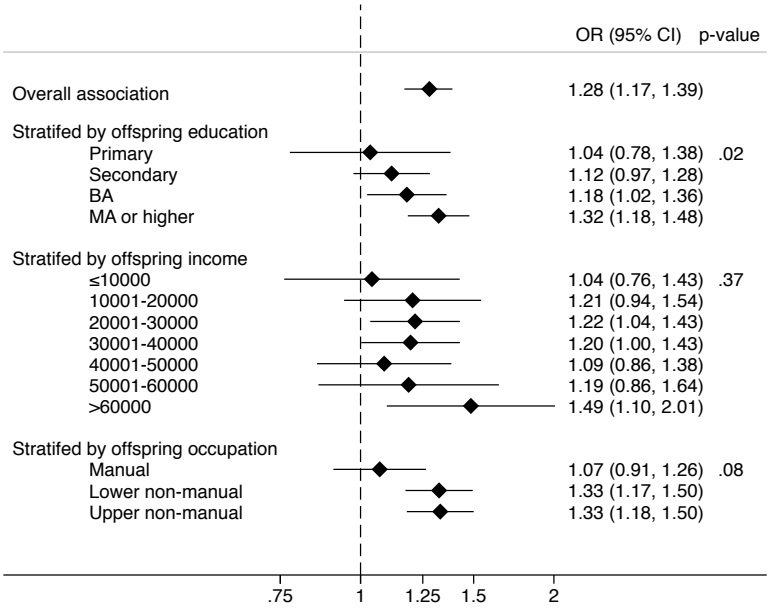

Figure 3. Odds ratios for associations of parental ideal health behaviors with ideal health behaviors among offspring stratified by offspring SEP in the Cardiovascular Risk in Young Finns Study

Abbreviations: SEP, socioeconomic position; BA, Bachelor's degree; MA, Master's degree; EUR, euro. Adjusted for the attrition indicator, sex, birth year, age, parental educational attainment and the interaction effect between the number of parental health behaviors and single-parenthood. Horizontal lines represent the 95% confidence intervals.

The odds ratios for the associations between parental ideal health behaviors and offspring ideal health behaviors were greater for offspring with higher educational attainment (**Figure 3**) or whose parents had higher educational attainment (**Figure 4**) than for those with lower educational attainment (p for linear trend = 0.02 (offspring education), p for trend = 0.01 (parental education)). Furthermore, the linear trends for both mother's and father's educational attainment were similar ($p_{\text{Wald heterogeneity}} = 0.45$). The association between parental ideal health behaviors and offspring health behaviors did not vary across levels of offspring income (**Figure 3**, p for trend = 0.37), but it seemed to be stronger at higher levels of parental income (**Figure 4**, p for trend = 0.06). The association of parental health behaviors with offspring health behaviors was also stronger among

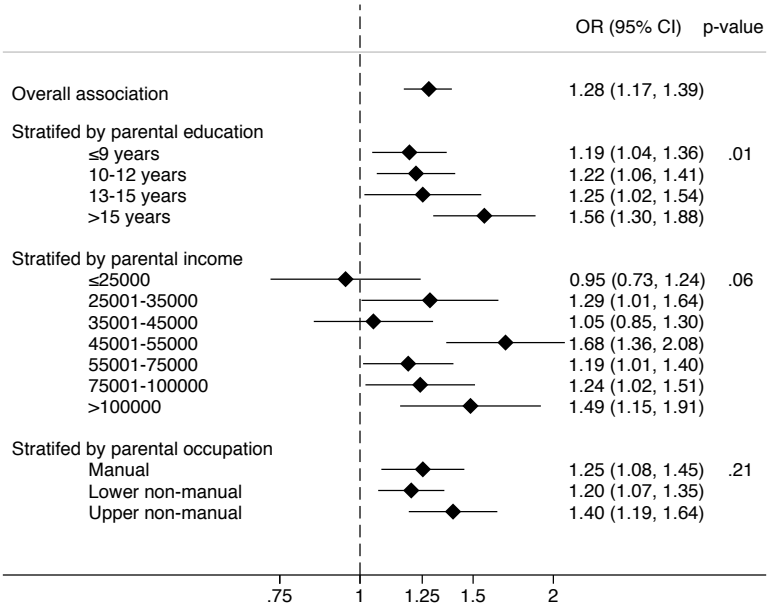

Figure 4. Odds ratios for associations of parental ideal health behaviors with ideal health behaviors among offspring stratified by parental SEP in the Cardiovascular Risk in Young Finns Study

Abbreviations: SEP, socioeconomic position; FIM, Finnish mark. Adjusted for the attrition indicator, sex, birth year, age and the interaction effect between the number of parental health behaviors and single-parenthood. Horizontal lines represent the 95% confidence intervals. Parental income measured as household gross income (FIM) in 1979.

offspring with higher occupational status (**Figure 3**, p for trend = 0.08). However, this trend was not consistently apparent with parental occupational status (**Figure 4**, p for trend = 0.21).

Similarly, in linear multilevel regression each one-unit increase in parental ideal health behaviors (equivalent to one additional ideal behavior in either parent) was associated with 0.08 (95% CI: 0.05, 0.11) units higher ideal health behaviors in their offspring after adjustments. These intergenerational associations were also greater among offspring with higher educational attainment (p for trend = 0.02) or whose parents had higher educational attainment (p for trend = 0.007) (**Figure 5**). Likewise, the intergenerational associations tended to be greater at higher levels of parental income (p for trend = 0.05) or offspring occupational status (p for trend = 0.07), but they did not differ across levels of offspring income (p for trend = 0.34) and parental occupational status (p for trend = 0.15).

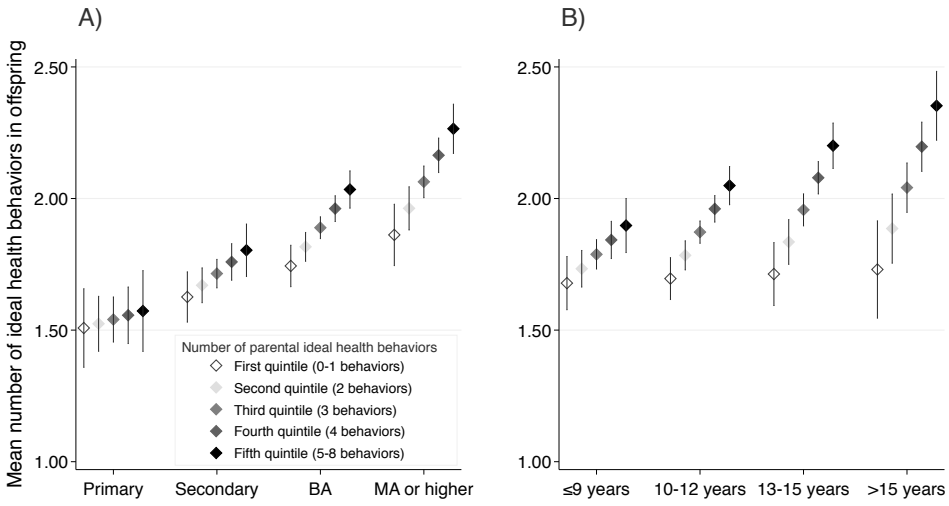

Figure 5. Mean number of offspring ideal health behaviors associated with parental health behaviors at different levels of A) offspring and B) parental educational attainment in the Cardiovascular Risk in Young Finns Study

Abbreviations: BA, Bachelor's degree; MA, Master's degree. Adjusted for the attrition indicator, sex, birth year, age and the interaction effect between the number of parental health behaviors and single-parenthood. Second panel additionally adjusted for parental educational attainment. Vertical lines represent the 95% confidence intervals.

All results were similar in analyses restricting the study population to participants from two-parent families (n = 1670).

4.3 Associations of childhood psychosocial environment with cardiac structure and function (Study III)

Table 5 shows the characteristics of the study participants. Unadjusted linear regression analyses showed that the favorable childhood psychosocial score was associated with lower LV mass and E/e' ratio. One standard deviation difference in the childhood psychosocial score was associated with 0.83 g/m$^{2.7}$ difference in LV mass (95% CI, -1.27 to -0.38) and 0.08 difference in E/'e ratio (CI=-0.15 to -0.01). These associations remained significant after adjusting for age and sex (b=-0.66, 95% CI, -1.09 to -0.23 for LV mass, b=-0.08, 95% CI, -0.15 to -0.02 for E/'e ratio) and age, sex and adult SEP (b=-0.52, 95% CI, -0.96 to -0.08 for LV mass, b=-0.08, 95% CI, -0.15 to -0.02 for E/'e ratio). The associations of the childhood psychosocial score with LV mass and E/e' ratio did not differ according to age (psychosocial score x age interaction p=0.79 for LV mass, p=0.63

Table 5. Characteristics of 880 participants from the Cardiovascular Risk in Young Finns Study (Study III)

	Mean (SD)	n [%]
Age in 2011	41.4 (4.9)	
Sex (women)		493 [56%]
Educational attainment in 2001		
No college		616 [70%]
College or higher		264 [30%]
Psychosocial factors in 1980		
Favorable socioeconomic environment (range, 0-4)	1.7 (1.2)	
Favorable emotional environment (range, 0-4)	2.5 (0.9)	
Favorable health behaviors of parents (range, 0-6)	4.9 (1.1)	
Lack of stressful events (range, 0-5)	4.8 (0.5)	
High self-regulatory behavior (range, 0-7)	6.7 (0.7)	
High social adjustment (range, 0-2)	1.5 (0.7)	
Childhood psychosocial factors score	0.7 (2.6)	
Ideal health behaviors in 2001		
≥2 ideal behaviors		613 [70%]
<2 ideal behaviors		267 [30%]
Non-smoking		608 [69%]
BMI <25 kg/m^2		519 [59%]
Ideal physical activity		480 [55%]
Ideal diet		231 [26%]
Left ventricular mass (g/m$^{2.7}$)	30.4 (6.7)	
E/e' ratio	4.8 (1.0)	

All values except for left ventricular mass (LV) (n=853) and E/e' ratio (n=860) calculated for participants with data on LV mass, E/'e ratio or both (n=880).
Mean LV mass (g/m$^{2.7}$) 29.6 (SD=6.2) and 31.2 (7.1) among those above vs below the median of the childhood psychosocial score.
Mean E/e' ratio 4.7 (0.9) vs 4.9 (1.0) among those above vs below the median of the childhood psychosocial score.

for E/e' ratio) or sex (psychosocial score x sex interaction p=0.52 for LV mass, p=0.34 for E/e' ratio). Those with childhood psychosocial score above the median had 84% higher sex- and age-adjusted odds for having 2 or more ideal health behaviors in adulthood compared to those below the median (OR=1.84, 95% CI, 1.35, 2.51). Having two or more ideal health behaviors in adulthood was associated with 2.17 g/m$^{2.7}$ lower LV mass (95% CI, -3.14, -1.20) and 0.23 lower E/e' ratio (95% CI, -0.38 to -0.09) compared to having less than two ideal behaviors after adjusting for sex, age, childhood psychosocial environment and adult SEP.

Table 6. Differences in LV outcomes between those above and below the median of childhood psychosocial score

	Complete cases	
	LV mass (g/m$^{2.7}$) Difference (95% CI)	**E/e' ratio** Difference (95% CI)
Linear regression		
Unadjusted	-1.61 (-2.51, -0.71)	-0.15 (-0.28, -0.02)
Sex- and age-adjusted	-1.16 (-2.02, -0.29)	-0.16 (-0.29, -0.03)
Marginal structural model[a]		
Total effect	-1.28 (-2.63, 0.07)	-0.18 (-0.39, 0.03)
Direct effect	-0.98 (-1.97, 0.00)	-0.14 (-0.29, 0.01)
Indirect effect	-0.30 (-1.22, 0.63)	-0.04 (-0.18, 0.11)
	Multiple imputation	
	LV mass (g/m$^{2.7}$) Difference (95% CI)	**E/e' ratio** Difference (95% CI)
Linear regression		
Unadjusted	-1.67 (-2.34, -1.01)	-0.17 (-0.26, -0.07)
Sex- and age-adjusted	-1.37 (-2.01, -0.72)	-0.16 (-0.25, -0.06)
Marginal structural model[a]		
Total effect	-1.36 (-2.27, -0.44)	-0.17 (-0.31, -0.03)
Direct effect	-1.05 (-1.74, -0.36)	-0.14 (-0.25, -0.04)
Indirect effect	-0.31 (-0.90, 0.29)	-0.02 (-0.12, 0.07)

Abbreviations: LV, left ventricular.

[a] Estimates from the marginal structural model adjusted for age, sex and time-dependent confounding by adult socioeconomic position (SEP).

Sample sizes differ due to available data (n=853 for LV mass, n=860 for E/e' ratio in the complete case analysis, n=1908 for LV mass, n=1939 for E/e' ratio after multiple imputation).

In complete case analysis, those above the median of the childhood psychosocial score had 0.90 g/m$^{2.7}$ lower LV mass (95% CI, -1.78, -0.02) and 0.16 lower E/e' ratio (95% CI, -0.29, -0.03) compared to those below the median of the childhood score after adjusting for age, sex and adult SEP.

In analyses with imputed data, those above the median of the childhood psychosocial score had 1.16 g/m$^{2.7}$ lower LV mass (95% CI, -1.34, -0.99) and 0.15 lower E/e' ratio (95% CI, -0.18, -0.12) compared to those below the median of the childhood score after adjusting for age, sex and adult SEP.

The differences in LV mass and E/e' ratio above and below the median of the childhood psychosocial score are presented in **Table 6**. The age- and sex-adjusted differences from linear regression models coincided with the total effect estimates from the marginal structural models controlling for age, sex and time-dependent confounding by adult SEP (total effect b=-1.28, 95% CI, -2.63, 0.07 for LV mass, b=-0.18, 95% CI, -0.39, 0.03 for E/e' ratio). The marginal randomized interventional analogue of the direct effect indicated a difference of 0.98 $g/m^{2.7}$ in LV mass among those above the median of the childhood score versus those below the median (95% CI, -1.97, 0.00). The analogue for the direct effect on LV diastolic function indicated a corresponding difference of 0.14 in E/e' ratio (95% CI, -0.29, 0.01). Approximately 23% and 21% of the associations of childhood environment with LV mass and E/e' ratio were estimated to be mediated through adult health behaviors (b=-0.30, 95% CI, -1.22, 0.63 for LV mass, b=-0.04, 95% CI, -0.18, 0.11 for E/e' ratio). However, these estimates were not statistically significant (natural indirect effect p=0.53 for LV mass, p=0.61 for E/e' ratio). (**Table 6**). Results with imputed data concurred with those from the primary analyses (**Table 6**). Although estimates for LV mass were somewhat greater, no indirect effects were observed in the imputed data.

5 DISCUSSION

This dissertation examined the life-course pathways of cardiovascular health and disease in relation to three intergenerational factors in the prospective Cardiovascular Risk in Young Finns Study. Study I examined the associations of a 97-SNP BMI genetic risk score with BMI development, and whether the genetic associations differ by SEP at different life stages. We found that higher genetic risk was associated with faster age-dependent increases in BMI, and that the genetic associations with mean levels of BMI across the follow-up were weaker for participants with higher adult SEP. Study II assessed the intergenerational associations of ideal cardiovascular health behaviors from parents to their offspring, and whether these associations differ by SEP at different life stages. Higher number of ideal health behaviors among parents was associated with higher number of ideal behaviors among their adult offspring. Moreover, the intergenerational associations of ideal health behaviors were greater for participants with higher own or parental SEP. In Study III, we demonstrated associations between favorable psychosocial environment in childhood and more optimal cardiac structure and function in adulthood. Results from causal mediation analysis showed no consistent evidence of health behaviors mediating the association of childhood psychosocial environment with cardiac structure and function in adulthood after accounting for adult SEP. Together these findings highlight the role of intergenerational and early-life exposures in initiating pathways of long-term cardiovascular health and suggest these pathways may be shaped by socioeconomic circumstances at different life stages.

5.1 Limitations

This study has limitations. Our data is from a long-running cohort study where loss to follow-up cannot be avoided. We conducted comprehensive attrition analyses in Studies I and II, and used pattern mixture modeling in Study II to account for the selective missingness. In Study III, we repeated the analyses in the sample after multiple imputation, obtaining similar findings to those from the complete cases analysis. However, selective loss to follow-up might have biased the estimates.

Like any observational study, we cannot rule out the possibility of unmeasured or residual confounding. However, we controlled for a set of potential confounders that were selected *a priori* based on their known or hypothesized relationships to the relevant exposures, outcomes and other covariates. Particularly strong assumptions regarding confounding pertain to the mediation analysis in Study III, as longitudinal settings often involve long time intervals between measurements of the

exposure and the mediator. This introduces the possibility of intermediate, time-dependent confounding of the mediator–outcome association.[70] We addressed the issue of time-dependent confounding by using recently developed methods for effect decomposition in the causal mediation framework. This approach is based on inverse probability weighting in marginal structural models, which requires estimating additional parameters – inevitably decreasing statistical power. The precision of the estimates we obtained in our analysis may thus be compromised by the methodological approach we chose in order to accurately represent the underlying causal structure. Causal mediation analysis helped to improve the specification of the causal model, although the variables were dichotomous which decreased measurement precision.[98] Extending the marginal structural modeling approach to discrete variables with more than two levels and developing methods for stable estimation of weights with continuous exposures and mediators are important tasks to improve accuracy of effect decomposition and enhance assessment of mediation in longitudinal settings.

The AHA cutoffs especially for diet and physical activity are relatively crude, and may not capture these health behaviors in sufficient detail. The adult FFQs used in this study have been validated in the Finnish population[23,99] and the dietary measures in childhood and adulthood have been associated with cardiovascular risk factors and outcomes.[100,101] Still, dietary intake could be incorrectly estimated due to assumptions of the food composition database or reporting bias. Self-reported measures of physical activity are potentially subject to reporting bias, however, the physical activity questionnaire used in this study has been shown to have acceptable convergent validity against objectively assessed pedometric data among Finnish adults.[102]

Although no established standard currently exists for measuring childhood psychosocial environment, the six factors included are theoretically sound[103,104] and have been associated with relevant cardiometabolic outcomes.[26,35,59–67] Likewise, no clear cutoffs exist for defining favorable vs adverse psychosocial experiences, and the childhood score cannot fully differentiate the relative contributions of beneficial vs adverse aspects of childhood environment.

The study participants were a cohort of predominantly white, ethnically homogeneous people residing in Finland, which may limit the generalizability of our results. In Study I, we did not limit our analysis to the SNPs identified in the European descent GWAS meta-analysis sample only, but used the total of 97 SNPs identified in European, African and east Asian descents. Although the

common BMI-associated variants have been found to show comparable effects across ancestries,[15] some independent risk-associated SNPs may differ in these populations.

5.2 Genetic and environmental associations across socioeconomic contexts – comparisons with literature

Cardiovascular disease runs in families, and the intergenerational etiologies involve both genetic and environmental factors. Studies I and II examined the intergenerational associations of CVD risk factors, first in regard to the genetic basis of BMI and then using a composite measure of health behaviors recorded from both parents and their offspring. In Study I, we demonstrated genetic associations with BMI trajectories over adulthood, finding that higher genetic risk, measured by 97 SNPs across the genome, was associated with more rapid increase in BMI with age. In Study II, we found that the total number of ideal health behaviors in parents was associated with the number of ideal behaviors among their offspring, with one additional ideal behavior in parents associated with 28% higher odds of their offspring having one additional ideal behavior. These findings concur with previous studies.[17–21,105]

Furthermore, we observed that both the genetic and behavioral associations differed across levels of SEP. Previous studies have suggested that obesogenic exposures, such as non-optimal diet,[40,41] sedentary behaviors[42,43] or mental health problems[42] accentuate the genetic associations with BMI. Such exposures are socioeconomically distributed, and thus stronger genetic associations might be expected to occur in disadvantaged environments. Consistent with this hypothesis, two recent studies in the UK Biobank using 69- and 94-SNP risk scores observed greater associations of polygenic risk scores with BMI among those at higher levels of social deprivation, with lower number of vehicles in the household and lower total household income.[39,42] While twin studies have suggested that the genetic associations with BMI also differ across educational attainment in adulthood, studies using molecular genetic measures of genetic risk have provided mixed evidence. While two previous studies using the 66-SNP and 32-SNP risk scores did not show evidence for interactions with education,[39,106] a recent study drawing on SNPs identified in the most recent GWAS meta-analysis reported stronger genetic associations at lower levels of education.[107] With the 97-SNP risk score, our findings suggest educational attainment is also a relevant indicator of SEP that influences the magnitude of genetic associations with adult BMI and that attaining higher educational level in adulthood may offset the expression of genetic risk of BMI.

While the genetic associations with BMI differed across levels of adult educational attainment, we observed no interaction effects between the genetic risk and parental educational attainment. These findings concur with a previous study conducted in our dataset that reported no interaction effect between a 32-SNP risk score and childhood SEP on BMI.[51] However, contrasting evidence has suggested that an interaction effect between genetic predisposition and early-life socioeconomic or obesogenic environments occurs among children and youth.[48,108] We additionally assessed effect measure modification by parental educational attainment in a subsample of participants <18 years of age, but found no evidence for interaction effects. Further studies with comprehensive polygenic measures of genetic risk are needed to determine whether childhood SEP interacts with genetic predisposition to high BMI. As overweight established in childhood is known to track into adulthood,[24] such knowledge is essential to evaluate rationales for primary prevention.

In Study II, intergenerational associations of ideal health behaviors differed across levels of childhood and adult SEP. We observed greater intergenerational associations of ideal behaviors at higher levels of parental and offspring's own adulthood education. Additionally, we observed greater intergenerational associations among participants who had higher occupational status or whose parents had higher income. Few previous studies have evaluated the role of SEP in influencing the intergenerational patterns of health behaviors and the results are not conclusive.[19,57,58] Our results are consistent with findings of Næss et al. (2016)[19] reporting weaker associations of parental overweight with offspring BMI in strata of higher parental education in a Norwegian cohort, suggesting that higher educational attainment is protective against the intergenerational transmission of higher BMI. By contrast, a study in the National Longitudinal Survey of Youth reported stronger rather than weaker intergenerational persistence of high BMI among participants with higher parental educational attainment.[58] Another study using the National Health Interview Survey, National Longitudinal Survey of Youth and the National Longitudinal Survey of Adolescent Health observed no interaction effects with education when examining intergenerational transmission of BMI.[57] Recently in our data, Serlachius et al. (2016)[109] showed that social support in adulthood was protective against the intergenerational risk for higher BMI. Our results show a similar pattern of interaction with both childhood and adult SEP for a set of ideal health behaviors defined by AHA.

5.3 Explanations for socioeconomic differences

Socioeconomic position is a proxy for a variety of environmental exposures that are relevant to several health outcomes. In general, higher SEP involves financial access to healthy lifestyles,

residence in neighborhoods promoting healthy behavioral options, more social support and less environmental stress, more extensive health-related knowledge and better psychological capability to act on this knowledge.[45,46,82,110] All these factors may influence both the genetic and behavioral associations of CVD risk factors.

Previous research has suggested that obesogenic environments amplify the expression of genetic risk of BMI.[39,42] We observed differences in genetic associations across levels of adult educational attainment. This likely reflects the socioeconomic patterning of obesogenic exposures. We further assumed ideal diet and ideal physical activity partially explain the educational differences in genetic associations. However, we saw no evidence for diet or physical activity explaining the differences. Although we did not formally assess mediation, our findings are consistent with a recent analysis of Tyrrell et al.[39] concluding that instead of any single aspect of an obesogenic environment, it is the composite environment that is the most plausible effect modifier of the genetic associations with BMI. Socioeconomic context is a feasible proxy for such composite environment as socioeconomic factors can determine the exposure to several factors that are associated with differences in BMI. Besides diet and physical activity, the explanatory pathways may involve factors such as mental health, psychosocial resources and stress-related physiological changes. The accumulation of multiple socioeconomically distributed exposures may determine differences in an overall environmental stress-burden,[110–113] which can explain the educational differences in genetic associations we observed.

Socioeconomic position can have similar implications for the intergenerational transmission of health behaviors. Higher SEP has been associated with higher reserve capacity – a generic protective influence on health through resources available to an individual that help maintain optimal functioning and healthy status.[114,115] Parental socioeconomic advantage can help create a developmental environment supporting optimal behaviors that has a lasting influence on offspring health behaviors. Furthermore, parents from more advantaged backgrounds may have more resources and knowledge that reduce the likelihood of parents passing on their non-ideal behaviors to their offspring. Higher SEP among offspring, in turn, involves greater access to healthy lifestyles occurring in advantaged environments that can help offspring maintain optimal health behaviors adopted in childhood and youth in later life stages. Higher SEP may also enhance a person's capability to access and use heath information.[46] Healthy behaviors of parents are one source of health promotion and people with higher SEP may more likely adhere to such examples. Higher educational attainment, in particular, has been associated with greater human capital, effective

agency and sense of personal control, more extensive health-related knowledge and better psychological capability to act on this knowledge.[46] Such factors may be especially important to an individual's ability to promote and maintain healthy behaviors.[46] It is also possible that the intergenerational associations of health behaviors involve genetic determinants. Our design was not genetically informative, but our findings may reflect higher SEP strengthening protective genetic associations.

Our findings from Studies I and II differ in terms of the timing of the effect measure modification by SEP. While the intergenerational associations of health behaviors were different across both parental and offspring adult SEP, the genetic associations differed only by offspring adult SEP. To some extent, these differences may reflect distinct mechanisms underlying the genetic and behavioral associations. While genetic associations reflect strongly biological pathways, intergenerational associations of health behaviors also involve processes of modeling and social learning and may thus be more readily liable to the influence of parental SEP or the broader socioeconomic context in childhood. Although our results suggest the genetic associations with BMI are primarily modified by socioeconomic factors in adulthood, other studies have presented contrasting evidence demonstrating that childhood obesogenic exposures may also accentuate the genetic risk of higher BMI.[48,108] More research is needed to understand the timing of the effect modifiers in the genetic associations with BMI.

5.4 Childhood psychosocial environment and adult cardiac outcomes

Previous studies have demonstrated associations of psychosocial factors in childhood with several important cardiometabolic risk factors in adulthood.[30–33,35,61] The results of Study III extend these findings to LV mass and diastolic function. Increased LV mass and LV diastolic dysfunction measured as the filling pressure of the left ventricle have been found to be prognostic of the risk of cardiovascular events and premature morbidity, independently of cardiovascular comorbidities and beyond traditional risk factor assessment, and thus they are clinically relevant markers for cardiovascular risk stratification.[116–118] An increase of 11.8 $g/m^{2.7}$ in LV mass has been associated with 40% increased rate of adverse cardiovascular events.[119] We observed a difference of 1.2 $g/m^{2.7}$ between those with unfavorable vs favorable childhood score, which would thereby correspond to 3% higher rate of cardiovascular events. Although the incubation time from childhood exposures to disease manifestation may be long, some evidence suggests that childhood psychosocial exposures are associated with progression of cardiovascular risk factors over time.[26,33] Future studies with

repeated measurements of cardiac structure and function are needed to elucidate the timing of etiologically relevant pathophysiological changes.

Several pathways can connect childhood environment with adulthood cardiac health. Childhood and youth are developmental periods during which important regulatory systems and physiological responses are programmed.[8,68] Childhood psychosocial environment may initiate differences in immune, metabolic, neuroendocrine and autonomic nervous systems relevant to cardiovascular health across life.[68] Behavioral factors are suggested as a potentially important, modifiable mechanism explaining the association of childhood psychosocial environment with cardiovascular outcomes.[27,34,68] However, the extent to which this occurs is not well understood.[68] We used marginal structural models to assess the associations of childhood environment with adult cardiac outcomes through ideal cardiovascular health behaviors while controlling for time-dependent confounding by adult SEP. After accounting for age, sex and adult SEP, there was no evidence of an indirect association of childhood environment with LV mass and diastolic function through ideal cardiovascular health behaviors. Nevertheless, health behaviors are considered as a major contributor of the socioeconomic gradient in health. A pathway from childhood environment to LV mass and diastolic function may involve a sequence of exposures,[8] whereby childhood environment influences adult SEP which in turn drives the association of health behaviors with cardiac outcomes. This is feasible given that some evidence suggests an indirect association from childhood environment to adult cardiovascular outcomes through adult SEP.[61,65] Furthermore, a recent study examining associations of childhood psychosocial adversity with adult cardiac outcomes did suggest an indirect association through health behaviors.[65] A relevant question is whether favorable and adverse childhood exposures tap into different intermediate mechanisms, with the role of health behaviors possibly accentuating with childhood adversity. Further research recognizing potentially distinct pathways initiated by favorable vs adverse early-life exposures is needed to explain the psychosocial origins of lifetime cardiovascular health.

5.5 Conclusions

Cardiovascular etiologies are complex, shaped by numerous factors acting together across life. The objective of this dissertation was to elucidate the role of three intergenerational factors in the life-course development of cardiovascular health. A few final notes deserve attention.

First, early-life factors initiate pathways leading to cardiovascular health and disease over the life-course. We demonstrated such associations in terms of genetic and behavioral determinants as well

as psychosocial context in childhood. Understanding the operation of early-life factors in determining life-course development of cardiovascular health is important to provide actionable evidence on effective primary prevention and cardiovascular health promotion from the earliest possible stages. Second, pathways of cardiovascular health initiated in early life stages are not deterministic. In this dissertation, we showed that the later-life expression of risk and protective factors of childhood and adolescence may be shaped by social factors occurring in adulthood. This notion of reversibility builds on evidence that has identified factors that can counteract the effects of risk exposures initiated in earlier life stages. An important task of further research is to elucidate intervention targets with potential to reverse pathogenic developments as well as determine effective windows of intervention. Finally, social determinants are ubiquitous to the life-course development of cardiovascular health. Understanding the social, economic and psychosocial realities people live in can, on one hand, help us identify individuals at risk – those to whom preventive actions should be targeted in particular. Also, it can inform us about the social barriers that can potentially severely hinder intervention efforts. Mitigating health inequality is an imperative that motivates further research to assess the variety of mechanisms through which social factors affect cardiovascular health over the lifespan.

The life-course perspective allows us to identify developmental periods and components of cardiovascular health that may drive positive and negative trajectories of cardiovascular health from childhood to adulthood. Together the findings of this dissertation highlight the relevance of the life-course perspective to cardiovascular health and healthy longevity. Further work is needed to evaluate these associations in other populations, elucidate the underlying mechanisms and assess the relevance of these findings to cardiovascular health promotion.

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